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09/333,248 06/15/99 VAN DER KOOY

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EXAMINER

YUCEL, I

ART UNIT

PAPER NUMBER

1636

DATE MAILED:

07/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.
09/333,248

Applicant
Van Der Kooy et al.

Examiner
Remy Yucel

Group Art Unit
1636



- ☐ Responsive to communication(s) filed on _____.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-4 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-4 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of References Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4
- ☐ Interview Summary, PTO-413
- ☒ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Claims 1-4 are pending in the application.

Claim Objections

Claim 1 is objected to because of the following informalities: the dependencies of this claim are completely incorrect. It depends from itself as well as from a claim that follows it. It also lacks a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to methods of treating individuals (humans) with a degenerative disease, disorder or abnormal state of the retina or eye (various examples are recited in claim 4) comprising implanting retinal stem cells or retinal cells differentiated from retinal stem cells. The following factors have been considered in the rejection.

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The nature of the invention. The nature of the invention is *in vivo* treatment of individuals, especially humans with a wide spectrum of degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited to indicate the state of the prior art and the unpredictable nature of the invention. The art at the time of the invention did not recognize retinal stem cells or their use in treatment of degenerative disease, disorder or abnormal physical states of the eye/retina via *in vivo* transplantation. The art does, however, recognize the ability to transplant retinal epithelial cells (RPE cells) (either as a tissue-layer or as individual cells) into the eye of various different animal models, including mammals. RPE cells are one type of cell expected to differentiate from retinal stem cells.

Grisanti *et al.* (U) teach the transplantation of RPE cells. They teach that normal RPE cells transplanted into the subretinal space of mutant RCS rats survive and rescue photoreceptor cells otherwise destined to undergo degeneration. However, they state that the while these findings are encouraging, the ultimate goal of achieving long-term survival of RPE allografts remains elusive (page 1619). Grisanti *et al.* also teach that the eye has the rare characteristic of being an immunologically privileged site, but they also caution that the ocular immune privilege is not absolute and that immunologic recognition of allogenic or xenogenic tissues/cells result in the rejection of histoincompatible grafts. At page 1625, they teach that even autologous tissue/cells

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may be rejected if the immune system is not suppressed. They teach that RPE cells produce specific autoantigens which act as strong immunogens which trigger immune reactions that result in rejection of the RPE cells (see page 1624). They teach that ACAID may have a role as a possible fail-safe mechanism to limit the destructive autoimmune reactions in the privileged sites, but also teach that prolonged ACAID may be accompanied by other detrimental side effects such as fibrosis.

Enzmann *et al.* (V) teach that while transplantation of RPE cells from embryonic and non-embryonic origins in the subretinal space of different animal models, including the RCS rat has resulted in maintenance of retinal function for long periods of time, such transplantations in humans have yet to be shown to be effective. One reason for this is an immune response to the transplanted cells at the transplantation site. One can detect rejection, indicating that the eye is not absolutely an immunologically privileged site (see for example the abstract). These teachings corroborate those of Grisanti *et al.* discussed immediately above. At page 182, Enzmann *et al.* teach that while the immune reaction may be controlled with extensive therapies, transplantation in the subretinal space is not performed to improve the quality of life, not to save life. The extensive immunosuppression required may however, endanger the survival of the patient because of its serious side effects. They conclude that many immunological questions must be answered (it is noted that this reference was published two years after Applicant's effective filing date) before extensive efforts in patients are possible and before rejection is no longer a major barrier to success.

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Crafoord *et al.* (W) and Valtink *et al.* (X), both of which were published in 1999, three years after Applicant's effective filing date, fully corroborate the findings discussed above. They both teach mammalian systems in which strong immunological reactions develop over time which result in the rejection of the transplanted cells. They both teach that this is a significant hurdle that must be overcome before progress can be made in treating patients with disorders of the retina/eye.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. The specification is completely silent with respect to transplantation of retinal stem cells (isolated from the RPE) or cells that have differentiated from the RPE. The specification fails to teach *in vivo* transplantation of any of the above cell types. Because there is no teachings as to how one may achieve transplantation and the fate of the cells after transplantation; the specification also does not teach the treatment or amelioration of even a single degenerative disease, disorder or abnormal physical states of the eye/retina, such as those enumerated in claim 4. There are no teachings as to how the skilled artisan would overcome any of the obstacles recognized in the art (summarized above) to reliably and predictably treat any disorder of the eye/retina--especially those as widely varied as blindness (which may a result of optic nerve damage, as opposed to a damaged retina) and cancers of the retina. There is not even a suggestion in either the art or the instant specification as how retinal stem cells (isolated from the RPE) or cells that have differentiated from the RPE may treat disorders with a wide variety of etiologies (nerve damage, viral infection, neoplasia, etc.) The teachings of the specification may

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be characterized as speculative or prophet at best with regard to treatment of any condition of the eye/retina.

The breadth of the claims. As mentioned above, the claims are drawn to the treatment of any condition of the eye or retina via transplantation of retinal stem cells or cells that have differentiated from said cells.

The quantity of experimentation. The art recognizes several hurdles to successful transplantation of RPE cells to treat degenerative disorders of the retina, including the problems of immunological reactions which result in the rejection of cells that are transplanted into the eye/retina. The prior art is silent with respect to the transplantation of retinal stem cells, ostensibly because prior to Applicant's disclosure, mammalian retinal stem cells were unknown. Therefore, there is a high degree of unpredictability in the treatment of degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual. This is especially true for transplantation of retinal stem cells since the art did not recognize this at the time of the invention.

As discussed above, the specification does not provide teachings with regard to the *in vivo* transplantation of retinal stem cells or cells differentiated from retinal stem cells and their fate after transplantation. The specification also fails to teach the treatment or amelioration of even a single degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual.

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In order to practice the invention, the skilled artisan would turn to the prior art and teachings of the specification. However, as summarized in the previous two paragraphs, neither the prior art nor the specification provide teachings which enable the skilled artisan to treat degenerative disease, disorder or abnormal physical states of the eye/retina by transplantation of retinal stem cells or differentiated retinal cells into the eye/retina of the individual. Given the highly unpredictable nature of the invention, the skilled artisan would need to engage in empirical or trial and error experimentation to practice the claimed invention. First the skilled artisan would have to overcome the immune response problem that is well documented in the art, then the artisan would need to establish appropriate transplantation sites, appropriate cell numbers to for each condition found recited in the claims. In addition, the skilled artisan would need to develop appropriate assays to determine which protocols were efficacious (these assays would certainly vary with the condition to be treated). This level of experimentation would clearly be undue on the part of the skilled artisan and as such, the specification is not found to be enabling for the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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In claim 2, the recitation "the mammal" found in line 1 of the claim lacks antecedent basis.

Similarly, in claim 3, line 1, the recitation "the mammal" lacks antecedent basis.

In claims 2-4, it is not clear which degenerative disease, disorder or abnormal states Applicant wishes to treat. In claim 1, the method is drawn to treating degenerative disease, disorder or abnormal states of the **retina**, whereas claims 2-4 are drawn to treating said states of the **eye**. Thus, the recitation "degenerative disease, disorder or abnormal states of the of the eye" found in dependent claims 2-4 lack antecedent basis in claim 1. Applicant should amend the claims such that they are consistent.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6 (d)). The Group 1600 FAX numbers are (703) 308-4242 or (703) 305-3014. Unofficial faxes may be sent to the examiner at (703) 305-7939. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Remy Yucel, Ph. D. whose telephone number is (703) 305-1998. The

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examiner can normally be reached on Monday through Fridays from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Remy Yucel, Ph. D.
Primary Patent Examiner
Technology Center 1600
July 17, 2000